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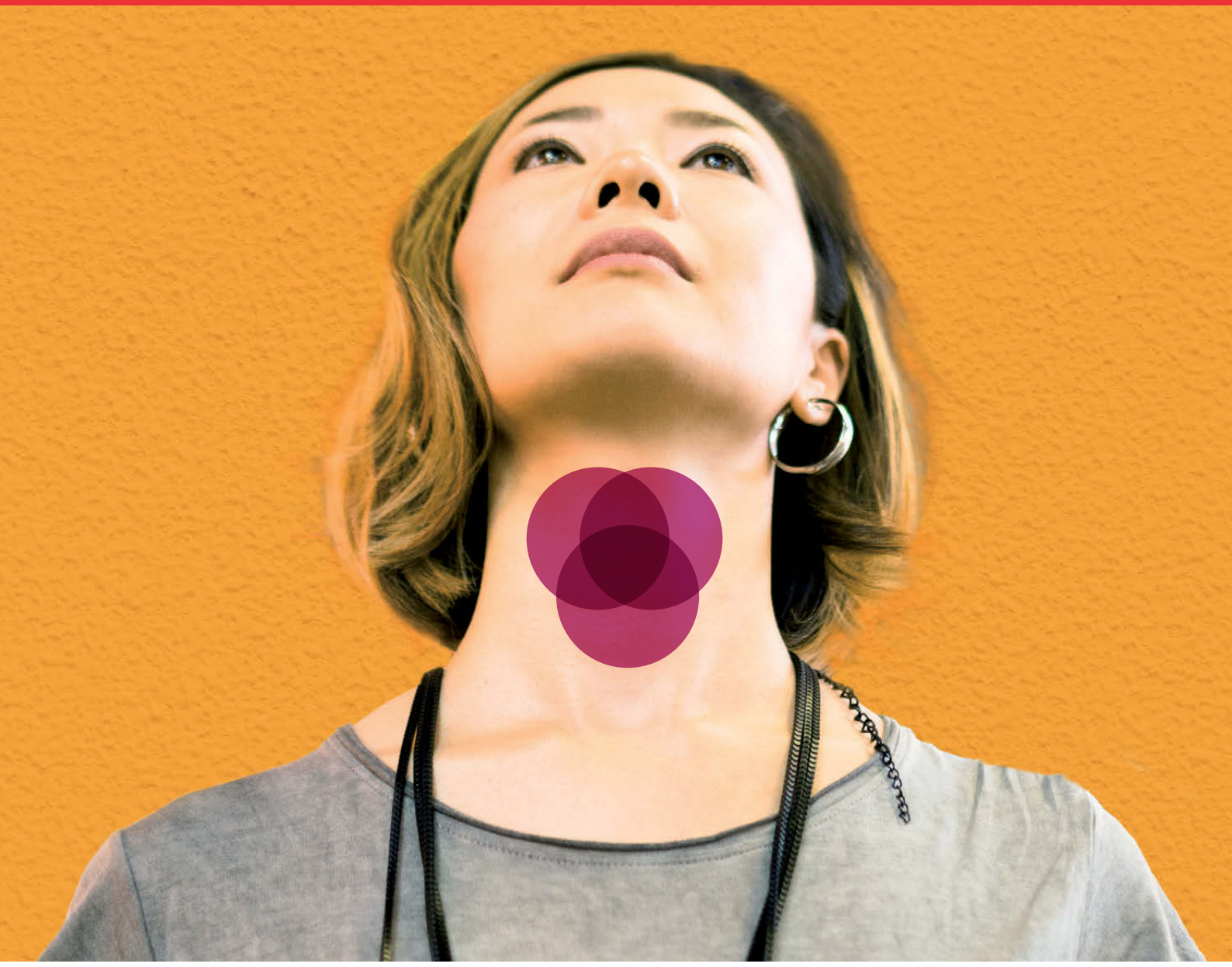

Improving differential diagnosis and follow-up in Graves' disease

B·R·A·H·M·S TRAK human Immunodiagnostic Assays

ThermoFisher SCIENTIFIC

TRAK human and human TSH receptor for reliable diagnosis

Human TSH receptor for unique clinical sensitivity

The design of Thermo Scientific™ B·R·A·H·M·S™ TRAK human assays is based on human TSH receptors that are expressed in a leukaemia cell line. For this reason the material is analogous to the TSH receptor in the human thyroid gland. Due to the high purity of the human TSH receptor, interferences with anti-Tg-antibodies and anti-TPO-antibodies can be ruled out.

The homologous B·R·A·H·M·S TRAK human assays, in conjunction with human antibodies as standards and human receptors, provide the most realistic reflection of the antigen/antibody interaction in humans.

The use of human TSH receptors in B·R·A·H·M·S TRAK human assays provides **superior clinical sensitivity (up to 98.8%) and specificity (up to 99.6%)** for the diagnosis of Graves' disease (Fig. 1).[1,2]

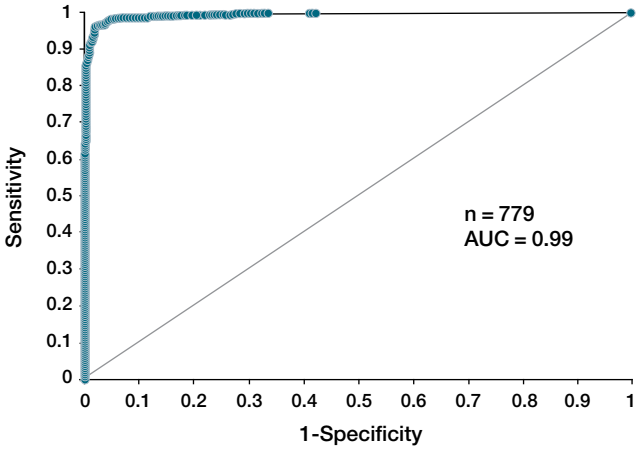

Figure 1 Receiver Operating Curve of B·R·A·H·M·S TRAK human KRYPTOR™ assay

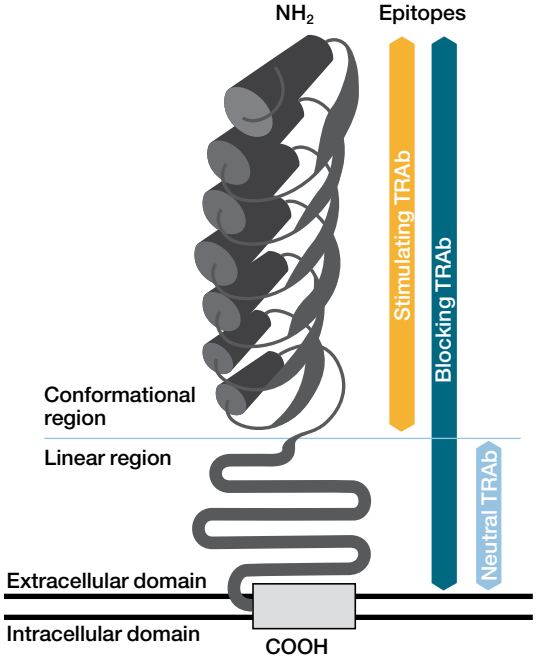

Figure 2 Domain structure of TSH receptor with epitopes for all 3 varieties of TSHR binding autoantibodies[mod. 4]

Stimulating and blocking antibodies

There are 3 different varieties of TSHR antibodies (TRAb) known: the stimulating, blocking and neutral type. While antibodies of the stimulating type bind exclusively to the conformational region of the receptor, the neutral TRAbs bind to the linear region. Blocking TRAbs bind to the entire extracellular part of the receptor (Figure 2), and thus cannot be distinguished from stimulating or neutral ones just based on the region of binding.[3,4]

While the stimulating TSHR antibodies are related to the Graves' induced thyrotoxicosis, this stimulating antibody population might change to a less stimulating or even blocking one or vice versa during the course of the disease.[5]

For a reliable follow-up of Graves' disease it is therefore important to monitor the full range of TRAbs in each patient. **With the human TSH receptor used, the B·R·A·H·M·S TRAK human assays detect all of the clinically relevant antibody types.**

TRAK human in the follow-up of patients with Graves' disease

Excellent prognostic value

It has been shown that TRAK human levels predict a relapse with high reliability (Fig. 3).[2,6,7] The positive predictive value was found to be 96.4% at 10 IU/L as early as 6 months of anti-thyroid drug therapy.[6] "End-of-treatment-cut-off" TRAK human of 3.85 IU/L had a prognostic value for relapse with a sensitivity of 85.3% (specificity 96.5%).[2] In addition, TRAK human values are associated with the severity of Graves' ophthalmopathy (GO) (Fig. 4).[8]

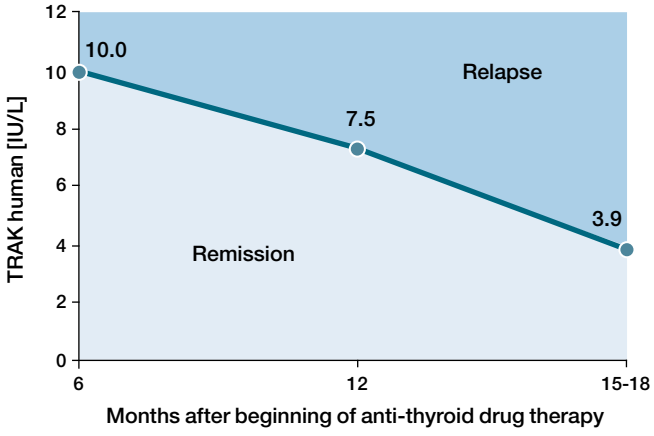

Figure 3 TRAK human cut offs for relapse[2,6,7]

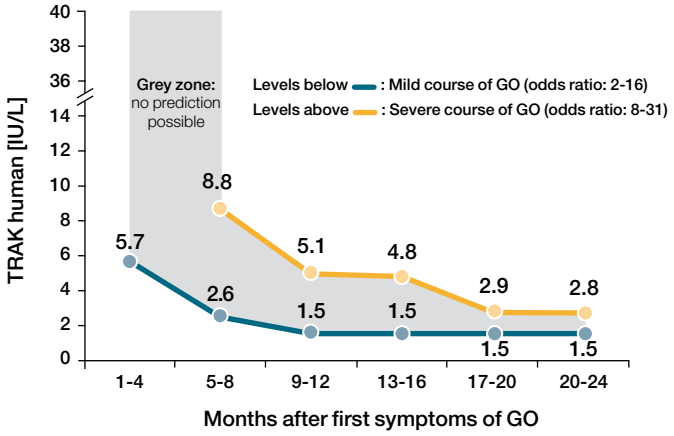

Figure 4 TRAK human cut offs for mild or severe course of Graves' ophthalmopathy (GO) [mod. 8]

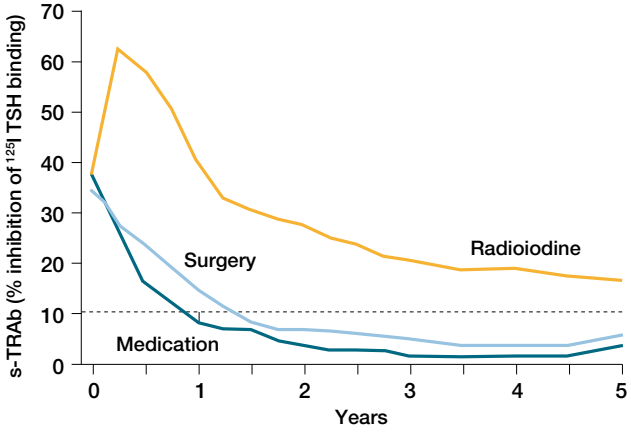

Figure 5 Different development of TRAb serum concentration over time depending on method of treatment[9]

Different treatment regimens

Antithyroid drugs are considered first-line therapy in patients with Graves' disease. Lifelong hypothyroidism, as it results from the ablative therapies, can be avoided here. However, as drug treated patients have high relapse rates thyroidectomy or ^{131}I-radiotherapy are viable second-line options.

For post-treatment surveillance the characteristic development of TRAb concentrations under different treatment regimens has to be taken into account (Fig. 5). In patients treated with medication or surgery, TRAb levels gradually decrease and reach the upper limit of the reference range (ULN) after 1 or 1.5 years. ^{131}I-radiotherapy induces a different pattern. TRAb levels increase considerably to a peak approx. 3 months after treatment followed by a gradual fall. During this treatment TRAb levels do not reach the normal reference limit for at least 5 years after treatment.[9]

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High discrimination in the differential diagnosis of patients with Graves' disease

The distribution of TSHR-Ab concentrations in different patient groups demonstrates the high discriminative power of the Thermo Scientific B·R·A·H·M·S TRAK human assays in various indications (Fig. 6). All TRAK human assays allow for dilution of out of range samples for best follow-up of the course of the disease. On the KRYPTOR instrument a fully automated dilution is provided.

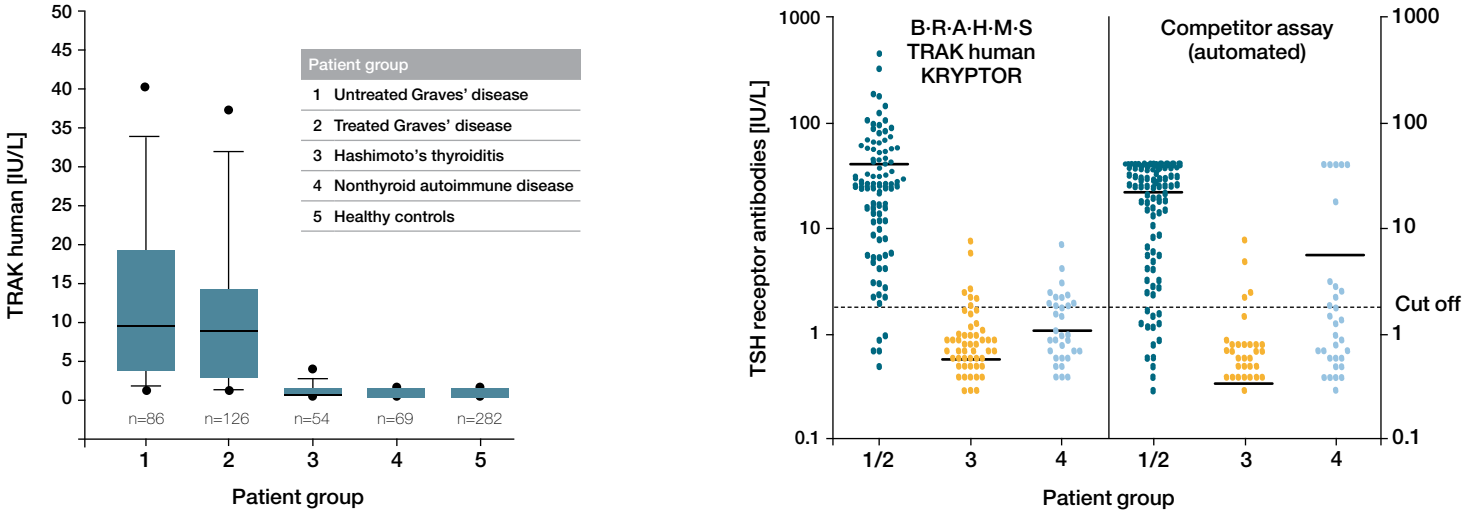

Figure 6 Distribution of TSH receptor antibodies in different groups of patients[1]

References

1. Costagliola, S., et al., *Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease.* J Clin Endocrinol Metab, 1999. 84(1): p. 90-7.
2. Carella, C., et al., *Serum thyrotropin receptor antibodies concentrations in patients with Graves' disease before, at the end of methimazole treatment, and after drug withdrawal: evidence that the activity of thyrotropin receptor antibody and/or thyroid response modify during the observation period.* Thyroid, 2006. 16(3): p. 295-302.
3. Morgenthaler, N.G., S.C. Ho, and W.B. Minich, *Stimulating and blocking thyroid-stimulating hormone (TSH) receptor autoantibodies from patients with Graves' disease and autoimmune hypothyroidism have very similar concentration, TSH receptor affinity, and binding sites.* J Clin Endocrinol Metab, 2007. 92(3): p. 1058-65.
4. Morshed, S.A. and T.F. Davies, *Graves' Disease Mechanisms: The Role of Stimulating, Blocking, and Cleavage Region TSH Receptor Antibodies.* Horm Metab Res, 2015. 47(10): p. 727-34.
5. McLachlan, S.M. and B. Rapoport, *Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa.* Thyroid, 2013. 23(1): p. 14-24.
6. Schott, M., et al., *Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease.* Horm Metab Res, 2004. 36(2): p. 92-6.
7. Eckstein, A.K., et al., *Patients with severe Graves' ophthalmopathy have a higher risk of relapsing hyperthyroidism and are unlikely to remain in remission.* Clin Endocrinol (Oxf), 2007. 67(4): p. 607-12.
8. Eckstein, A.K., et al., *Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease.* J Clin Endocrinol Metab, 2006. 91(9): p. 3464-70.
9. Laurberg, P., et al., *TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study.* Eur J Endocrinol, 2008. 158(1): p. 69-75.

Clinical Diagnostics

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